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L2: Entry 20 of 35 File: USPT Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994110 A
TITLE: Methods for direct synthesis of compounds having complementary structure to a desired molecular entity and use thereof

ABPL:
Compounds which possess a complementary structure to a desired molecule, such as a biomolecule, in particular polymeric or oligomeric compounds, which are useful as in vivo or in vitro diagnostic and therapeutic agents are provided. Also, various methods for producing such compounds are provided. These polymeric or oligomeric compounds are useful in particular as antimicrobial agents, receptor, hormone or enzyme agonists and antagonists.

BSPR:
The present invention pertains to methods for the direct synthesis of compounds, e.g., polymeric or oligomeric compounds, that possess a complementary structure to a desired template molecule, e.g., a compound having biological activity. The present invention further pertains to compounds, e.g., polymers or oligomers produced by such methods, and the use thereof, e.g., as therapeutics or diagnostics based on their complementary structure to a molecule having a known activity. The direct synthesis methods provided herein, which are an extension of the technique generally known as "molecular imprinting," provide a powerful means of producing a compound having a desired activity. While the technique should be applicable for the synthesis of a complementary binding molecule to any desired compound, the most significant application comprises direct drug synthesis. As discussed in detail infra, the subject invention is particularly useful for direct synthesis of agonists or antagonists for desired molecules, e.g., enzymes, hormones, receptors and other proteins; molecules that affect gene expression, molecules that affect the binding of biomolecules; e.g., cells or cell-like moieties to other ligands; and the synthesis of improved diagnostic agents.

BSPR:
Toward that end, the present inventors have developed a highly efficient means of directly synthesizing a compound, in particular a polymer or oligomer having a desired function, typically a biological activity, that enables such compound to be used as a drug, catalyst, competitive affinity ligand inhibitor, competitor, agonist, antagonist, or diagnostic agent. The present inventors have in particular developed a highly efficient means for the direct synthesis of compounds, e.g., polymers or oligomers, that possess a complementary structure to a desired molecular entity, typically a biomolecule, or portion thereof, e.g., the active site, that are useful, e.g., as agonists or antagonists of enzymes, hormones, receptors, for regulating gene expression, as antimicrobial or antiviral agents, as reaction catalysts, and in general for any activity which relies upon the ability of a compound to bind to another moiety based on its complementary structure.

BSPR:
Another object of the invention is to provide compounds, e.g., polymers or oligomeric compounds, that are complementary in structure to desired molecules or portions thereof, in particular the active site(s). These molecules included in particular biomolecules such as enzymes, receptors, hormones, growth factors, cytokines, antibodies, antigens, lectins, biological cells, cell vesicles, nucleic acid sequences, peptides, glycoproteins, carbohydrates, and fragments thereof.

BSPR:
A more specific object of the invention is to provide compounds, e.g., oligomers

or polymers, that are complementary in structure to a desired molecule or portion thereof, e.g., the active site(s) thereof, which may be used, e.g., as agonists and antagonists of enzymes, hormones or receptors; modulators of gene expression, catalysts, therapeutic agents, diagnostic agents, antimicrobial agents, antiviral agents, anti-tumor agents, affinity separation medium, or competitive affinity ligands.

DRPR:
FIG. 2 depicts schematically the production of a polymeric or oligomeric compound having a complementary structure to a biomolecule, e.g., an enzyme, receptor or antibody. In this schematic, monomers or other molecules are allowed to align along the surface or active site of a biomolecule, based on their complementary structure to residues on the biomolecule. These residues may comprise endogenous functional groups which alternatively may be derivatized. After alignment, these monomers are polymerized, optionally in the presence of a crosslinking agent. The biomolecule is removed to produce a thin-layer polymeric or oligomeric compound that exhibits a complementary structure to the active site of the biomolecule.

DEPR:
Relationship of Molecular Structure to Function The present invention is based in part on the fact that the activity of molecules, and in particular biomolecules, is correlated to their structure, which affects their ability to specifically interact with other molecules, e.g., receptors, hormones, enzymes, nucleic acid sequences, and microorganisms.

DEPR:
Generally, it is only specific residues of the compound which interact with other moieties, e.g., other biomolecules. These residues are generally on the surface of the particular compound, e.g., an enzyme, biological cell, receptor, etc.

DEPR:
The present invention is based in part on the inventors' previous extensive research and knowledge in the area of molecular imprinting. This technique is reviewed in Biotechnology, Vol. 14, pp. 163-170 (February 1996), from which much of this discussion is based.

DEPR:
The concept of molecular imprinting is depicted in FIG. 1. The molecule to be imprinted is first allowed to form bonds with polymerizable entities, which are subsequently crosslinked. Following extraction of the print molecule, specific recognition sites are left in the polymer where the spatial arrangement of the polymer network corresponds to the imprinted molecule. These procedures make use of a high percentage of crosslinker resulting in the formation of rigid and insoluble macroporous polymers. This template-assisted assembly, leading to an artificial recognition matrix, is thus performed in a very direct way.

DEPR:
A large number of substances have been imprinted for various practical applications. Four main applications include the use of molecularly imprinted polymers: (i) as tailor-made separation materials, (ii) as antibody and receptor binding site mimics in recognition and assay systems, (iii) for catalytic applications as enzyme mimics, and (iv) as recognition elements in biosensors.

DEPR:
However, the use of such techniques for direct synthesis of drugs and in vivo prophylactic or diagnostic agents has not previously been suggested. Based on their extensive knowledge and expertise in molecular imprinting, the present inventors conceived the idea that it should be possible to directly synthesize a compound, e.g., a polymer or oligomer, that possesses a complementary structure to a desired compound, e.g., biomolecule, or portion thereof, and use the resultant compound in applications wherein a compound having a complementary structure to a biomolecule would be desirable, e.g. therapeutic applications. As discussed, the ability of most biomolecules to finction as therapeutic or diagnostic agents hinges upon its structure, and the interaction of such structure with other molecules. Therefore, the present invention provides compounds, e.g., polymers or oligomers, useful as drugs, both prophylactic and therapeutic agents and in vivo diagnostic agents. The compounds produced according to the invention are useful as therapeutic or diagnostic agents based on their ability to specifically interact with and affect the biological activity

of a particular biomolecule that possesses a complementary structure to such compound.

DEPR:
Thus, in the present invention, similar to molecular imprinting, polymerizable molecules are permitted to associate by complementary binding (non-covalent or covalent) to specific groups of a biological compound followed by polymerization. However, an important difference of the present invention is that the resultant polymers or oligomers form a coating or image around the biomolecule, which coating or image is removed therefrom, and discrete entities are derived therefrom, which may be used, e.g., as therapeutic or prophylactic agents, i.e., drugs.

DEPR:
Also, another important difference between the polymers or oligomers that result from the subject invention in relation to the products that result from traditional molecular imprinting methods is their size. In general, the polymeric or oligomeric compounds that result from the methods of the present invention will possess a molecular weight that ranges from about 1000 to 200,000, more preferably from about 5,000 to 50,000, and most preferably about 20,000 to 30,000. However, these ranges may dependent upon factors such as the particular method utilized to produce such compounds, the particular template molecule, and the intended application therefor. Generally, if the polymer or oligomer is to be utilized as an in vivo therapeutic or diagnostic, it will possess a molecular weight on the lower end of the above ranges. In general, polymers according to the invention will comprise over 100 repeat units and oligomers will comprise less than about 100 repeat units. This controls the molecular weight. As noted above, lower molecular weights are preferably particularly for therapeutic purposes wherein solubility and viscosity are a significant concern. The upper limit of the preferred molecular weight range will correspond to polymers having about 200-300 repeat units. However, this may vary dependent upon the particular monomers and the intended application thereof.

DEPR:
Another difference between the polymers or oligomers that result from the subject invention in relation to conventional molecular imprinting methods is their size. In general, the subject polymers or oligomers will be smaller. The specific size will vary dependent upon the particular method utilized. Preferably, the polymeric or oligomeric compounds will possess an average chain length ranging from 25 angstroms to 5000 angstroms, more preferably from about 250 to 2500 angstroms, and most preferably about 500 to 1500. This will vary depending upon the intended application. If the polymeric or oligomeric compounds are to be used therapeutically they will typically be of smaller size, e.g., from about 500 to 1000 angstroms, or smaller. Alternatively, the subject compounds can be used in vitro, e.g., as affinity separation media or competitive affinity ligands.

DEPR:
FIG. 3 depicts another preferred means of practicing the invention. In this method, a desired moiety ("print molecule") is immobilized to a support, e.g., a polyacrylamide gel or other support material. (Other support materials include by way of example silica, polysaccharides, organic polymers, metals, alloys and glass, et seq.). This molecule may be immobilized to the support by covalent or non-covalent means. After immobilization the support comprising an immobilized print molecule, e.g., an enzyme, receptor, nucleic acid sequence, or other biomolecule is contacted with a solution containing one or more monomers. The monomers are preferably selected such that they are functionally complementary to functional groups comprised on the immobilized print molecule. For example, if the print molecule contains positively charged moieties, then negatively selected monomers are preferably selected. Typically, the monomer containing solution will comprise crosslinkers.

DEPR:
As discussed, the subject invention provides compounds, i.e., polymers or oligomers, that exhibit a complementary structure to desired molecules, e.g., biomolecules, or portions thereof, e.g., the active site. These compounds are useful as in vivo or in vitro therapeutic or diagnostic agents based on their ability to affect the activity of a particular biomolecule, e.g., a protein, DNA, virus, receptor, hormone, enzyme glycoprotein, microbial cell, mammalian cell, etc. Also, these compounds may be used as competitive affinity ligand inhibitors,

competitors, agonists, catalysts, or antagonists. These uses are meant to be exemplary and not exhaustive of the applications of the compounds which result from the present invention. Essentially, the subject compounds can be used for any purpose wherein a compound having a complementary structure to another compound is useful.

DEPR:
Two approaches to the production of a molecular imprint polymer have been developed, and either can be used in the methods disclosed herein. In the first method, a biomolecule is covalently bound to a polymerizable monomer, and after polymerization, the covalent bond is cleaved to release the biomolecule from the polymeric coating. Using this method, a selected biomolecule is attached to a polymerizable moiety using any appropriate method. The polymerizable biomolecule should contain a linkage that can be broken to release the biomolecule after the polymeric compound is formed, without adversely affecting the complementary structure thereof The resultant polymer compound shall be cleavable into discrete entities suitable for in vivo use.

DEPR:
The subject compounds, dependent upon the particular molecule with which they are complementary, may be used by way of example as antagonists or agonists of hormones, receptors or enzymes; as modulators of gene expression, as antimicrobial compounds, as vaccines, as anti-tumor agents and as wound healing agents.

DEPR:
This example provides a means for preparing linear, templated polymers which bind specifically to integrins, which are cell-surface based proteins that are involved in cell-cell or cell-matrix interactions in biological processes.

DEPR:
The integrin .alpha..sub.lib .beta..sub.3 (1 mg), N-acryloyl L-arginine (5 mg), N-acryloyl L-glutamic acid (5 mg), acrylamide (50 mg) and TENED (5 .mu.L) are suspended in aqueous sodium phosphate buffer (1 mL, pH 7). The mixture is equilibrated at room temperature, degassed by purging with oxygen-free nitrogen and polymerization initiated by the addition of 10% w/v ammonium persulphate in water (100 .mu.L). After four hours the templated polymer is released from the integrin via the addition of the competing synthetic tripeptide RGD (100 mg) and the polymer isolated via fractional precipitation with saturated ammonium sulphate. The polymer is then purified via repeated precipitation from water into methanol.

DEPL:
Molecular Imprinting Technology

ORPL:
The Emerging Technique of Molecular Imprinting and Its Future Impact on Biotechnology, Biotechnology, vol. 14, pp. 163-170 (1996).

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L9: Entry 2 of 9 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756632 A
TITLE: Systems for premeating molecules of predetermined molecular weight range

BSPR:
Takahara, et al. discloses the preparation of Segmented Poly (etherurethaneureas) (SPUU) with hydrophilic and hydrophobic polyether components. (Takahara et al., "Surface Molecular Mobility and Platelet Reactivity of (SPUUS) with Hydrophilic and Hydrophobic Soft Segment Components", J. Biomater. Sci. Polymer. Edn. 1(1):17-29 (1989)). Platelet adhesion and dynamic contact angle measured after adsorption of bovine serum albumin revealed that the SPUUs with hydrophilic soft segments had a non-adhesive surface.

DEPR:
When permeation occurs by transport through "large" pores, e.g., greater than about 0.1 micron, the transmission rate through a microporous membrane is generally directly proportional to the film area and the concentration driving force. However, the transmission rate is affected far less by the thickness of the film than it is in monolithic films. On the other hand, the porosity of a microporous membrane is a major determinant of the permeability rate. A microporous membrane made from polyethylene, polycarbonate, polyvinylchloride or other polymers and copolymers which are glassy or crystalline at the use temperature, e.g., 37.degree. C., will transport polar permeants primarily through its pores. For that type of membrane, therefore, permeability increases and strength decreases with total porosity or void volume fraction.

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USPT	platelet.clm. sane coat$.clm.	150037	L2
USPT	platelet.clm. and coat$.clm.	537	L1

L5: Entry 97 of 98 File: USPT Dec 23, 1975

DOCUMENT-IDENTIFIER: US 3927422 A
TITLE: Prosthesis and method for making same

DEPR:
Evidence has been presented implying the formation of a complex between incomplete carbohydrate chains in collagen and glucosyltransferase present on the outer surface of platelets as the primary step resulting in platelet recognition of and subsequent adhesion to collagen. (Jamieson, G. A., Urban, L. C., and Barber, A. J.: Enzymatic basis for platelet: collagen adhesion as the primary step in haemostasis. Nature New Biology 234:5 (1971): Barber, A. J. and Jamieson, G. A.: Platelet collagen adhesion characterization of collagen glucosyltransferase of plasma membanes of human blood platelets. Biochim. Biophys. Acta 252:533 (1971)). The reaction involves the enzymatic coupling of glucose to galactosyl residues attached to hydroxylysine side chains incorporated into the collagen peptides. The glucose is supplied by platelets as uridinediphosphoglucose (UDPG) according to the following: ##SPC1##

DEPR:
Platelet aggregation activity of collagen in vitro has been shown to require the structural integrity of the 6-hydroxymethyl group of galactose and the .epsilon.-amino groups of lysine and hydroxylysine on the collagen molecule. It has been postulated that the substrate specificity of the platelet glucosyltransferase is responsible for these observed platelet aggregation dependent phenomena (Chesney, C., Harper, E., and Coleman, R. W.: Critical role of the carbohydrate side chains of collagen in platelet aggregation. HIEG 72-43 (1972); Wilner, G. D., Nossel, H. L., and LeRoy, E. C.: Aggregation of platelets by collagen. J. Clin. Invest. 47:2616 (1968)).

DEPR:
It is believed by some that the initial event leading to the formation of an intravascular mural thrombus is the unmasking of subintimal collagen and its subsequent recognition by circulating platelets with the latter's resulting adhesion and aggregation (this view is not universally accepted). It is known, however, that collagen is capable of initiating platelet adhesion to itself and that this adhesion can result in platelet aggregation. The precise biochemical mechanism by which platelets recognize collagen and subsequently adhere to it has been shown to involve the formation of a complex between incomplete carbohydrate side chains in collagen and glucosyltransferase present on the outer surface of platelets (see FIG. 1). The reaction involves the enzymatic coupling of glucose (supplied by the platelets as uridinediphosphoglucose) to galactosyl residues attached to hydroxylysine side chains incorporated into the collagen peptides.

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End of Result Set

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L9: Entry 2 of 2 File: DWPI Feb 16, 2001

DERWENT-ACC-NO: 1996-010669
DERWENT-WEEK: 200114

TITLE: Microparticle delivery system contg. organo:metallic silicone polymer - use esp. for immunogens, as for vaccination, diagnosis, and treatment of bacterial and viral infections, and can be given mucosally.

INVENTOR: BROOK, M A; HERITAGE, P L ; JIANG, J ; LOOMES, L M ; MCDERMOTT, M R ; UNDERDOWN, B J

PRIORITY-DATA: 1994US-0245646 (May 18, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
ES 2153034 T3	February 16, 2001	N/A	000	A61K009/58
WO 9531187 A1	November 23, 1995	E	056	A61K009/58
AU 9524419 A	December 5, 1995	N/A	000	A61K009/58
US 5571531 A	November 5, 1996	N/A	021	A61K009/56
EP 762875 A1	March 19, 1997	E	000	A61K009/58
EP 762875 B1	December 20, 2000	E	000	A61K009/58
DE 69519670 E	January 25, 2001	N/A	000	A61K009/58

INT-CL (IPC): A01N 25/34; A61K 9/14; A61K 9/50; A61K 9/56; A61K 9/58

ABSTRACTED-PUB-NO: EP 762875B
BASIC-ABSTRACT:

Particulate carrier comprising: (a) a solid core comprising a polysaccharide and a proteinaceous material; and (b) an organometallic polymer bound to the core; is new.

USE - The carrier is used, esp. in microparticle form, for delivery of bioactive materials to humans and other animals. These are partic. immunogenic materials, including proteins, peptides, antigens, antibodies, bacteria and viruses and their lysates, haptens, carbohydrates, nucleic acids, lipids and glycolipids, also other pharmacologically active materials, or their combinations, derivs. and mixts.. Examples of proteins are human or human serum albumin; of viruses are influenza, measles, mumps, HIV, polio, rubella, herpes simplex 1 and 2, hepatitis A, B, C, yellow fever, smallpox, rabies, vaccinia, rota-, rheo- and rhino-virus, Echo, Coxsackie, papilloma, and adenovirus. Lists of bacteria, and yeasts, are also included.

ADVANTAGE - The proteinaceous material, which may also be the bioactive material, can be incorporated into the carrier at temps. which do not denature or otherwise deactivate it. The organometallic coating provides protection and improved safety in manufacture, also improving ease of storage, without affecting biocompatibility. The protective coating also allows mucosal, e.g. oral and nasal, as well as normal parenteral delivery, and improved immunogenicity, partic. for antigens not normally giving a good response.

ABSTRACTED-PUB-NO:

US 5571531A
EQUIVALENT-ABSTRACTS:

Particulate carrier comprising: (a) a solid core comprising a polysaccharide and a proteinaceous material; and (b) an organometallic polymer bound to the core; is new.

USE - The carrier is used, esp. in microparticle form, for delivery of bioactive materials to humans and other animals. These are partic. immunogenic materials, including proteins, peptides, antigens, antibodies, bacteria and viruses and their lysates, haptens, carbohydrates, nucleic acids, lipids and glycolipids, also other pharmacologically active materials, or their combinations, derivs. and mixts.. Examples of proteins are human or human serum albumin; of viruses are influenza, measles, mumps, HIV, polio, rubella, herpes simplex 1 and 2, hepatitis A, B, C, yellow fever, smallpox, rabies, vaccinia, rota-, rheo- and rhino-virus, Echo, Coxsackie, papilloma, and adenovirus. Lists of bacteria, and yeasts, are also included.

ADVANTAGE - The proteinaceous material, which may also be the bioactive material, can be incorporated into the carrier at temps. which do not denature or otherwise deactivate it. The organometallic coating provides protection and improved safety in manufacture, also improving ease of storage, without affecting biocompatibility. The protective coating also allows mucosal, e.g. oral and nasal, as well as normal parenteral delivery, and improved immunogenicity, partic. for antigens not normally giving a good response.

A particulate carrier, which comprises:

a solid matrix comprising a polysaccharide and a proteinaceous material, and a functionalised silicone polymer bonded to the matrix.

WO 9531187A

ABSTRACTED-PUB-NO: EP 762875B
EQUIVALENT-ABSTRACTS: Particulate carrier comprising: (a) a solid core comprising a polysaccharide and a proteinaceous material; and (b) an organometallic polymer bound to the core; is new. USE - The carrier is used, esp. in microparticle form, for delivery of bioactive materials to humans and other animals. These are partic. immunogenic materials, including proteins, peptides, antigens, antibodies, bacteria and viruses and their lysates, haptens, carbohydrates, nucleic acids, lipids and glycolipids, also other pharmacologically active materials, or their combinations, derivs. and mixts.. Examples of proteins are human or human serum albumin; of viruses are influenza, measles, mumps, HIV, polio, rubella, herpes simplex 1 and 2, hepatitis A, B, C, yellow fever, smallpox, rabies, vaccinia, rota-, rheo- and rhino-virus, Echo, Coxsackie, papilloma, and adenovirus. Lists of bacteria, and yeasts, are also included. ADVANTAGE - The proteinaceous material, which may also be the bioactive material, can be incorporated into the carrier at temps. which do not denature or otherwise deactivate it. The organometallic coating provides protection and improved safety in manufacture, also improving ease of storage, without affecting biocompatibility. The protective coating also allows mucosal, e.g. oral and nasal, as well as normal parenteral delivery, and improved immunogenicity, partic. for antigens not normally giving a good response. US 5571531A A particulate carrier, which comprises: a solid matrix comprising a polysaccharide and a proteinaceous material, and a functionalised silicone polymer bonded to the matrix. WO 9531187A

CHOSEN-DRAWING: Dwg.0/12 Dwg.1/16

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L3: Entry 51 of 247 File: USPT Jun 9, 1998

US-PAT-NO: 5763199
DOCUMENT-IDENTIFIER: US 5763199 A

TITLE: Platelet blockade assay

DATE-ISSUED: June 9, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Coller; Barry	New York	NY	N/A	N/A

US-CL-CURRENT: 435/7.21; 435/975, 436/527, 436/533, 436/69

CLAIMS:

What is claimed is:
1. A method of determining whether an individual has reduced ability to form platelet thrombi due to GPIIb/IIIa blockade, comprising the steps of:
a) obtaining a blood sample from the individual being assessed;
b) mixing the blood sample with 1) an anticoagulant; 2) sufficient buffer to maintain the pH and salt concentration of the anticoagulated blood within a range suitable for platelet aggregation; and 3) a platelet GPIIb/IIIa receptor ligand immobilized on a solid surface;
c) agitating the mixture formed in b) for a period of time sufficient for unblocked platelet GPIIb/IIIa receptors to bind with the platelet GPIIb/IIIa receptor ligands on said solid surface; and
d) assessing platelet-mediated agglutination in the agitated mixture, wherein the absence of agglutination indicates that the individual has reduced ability to form platelet thrombi.
2. The method of claim 1 wherein the GPIIb/IIIa receptor ligand is selected from the group consisting of fibrinogen, monoclonal antibody 10E5, monoclonal antibody c7E3, von Willebrand factor, fibronectin, vitronectin, and synthetic ligands having an arginine-glycine-aspartic acid (RGD) GPIIb/IIIa binding sequence.
3. The method of claim 1 further comprising the addition of a thrombin receptor activator in step b).
4. The method of claim 3 wherein the thrombin receptor activator is a thrombin receptor activating peptide.
5. The method of claim 4 further comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
6. The method of claim 4 wherein the thrombin receptor activating peptide is selected from the group consisting of (SEQ ID NOS: 1, 2, 4, and 7).
7. The method of claim 6 further comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
8. The method of claim 4 wherein the thrombin receptor activating peptide comprises a peptide resistant to inactivation by plasma aminopeptidase M.
9. The method of claim 8 wherein the thrombin receptor activating peptide comprises an N-terminal isoSer peptide.
10. The method of claim 9 wherein the N-terminal isoSer peptide is selected from the group consisting of (SEQ ID NOS: 3, 5, 6, and 8).
11. The method of claim 10 wherein the N-terminal isoSer peptide comprises isoSer-Phe-Leu-Leu-Arg-Asn (SEQ ID NO:3).
12. The method of claim 1 wherein the solid surface comprises glass microparticles or small polymeric beads, the surface of said microparticles or beads modified with a GPIIb/IIIa receptor ligand.

13. The method of claim 12 wherein the small polymeric beads have diameters from about 1 to about 6 .mu.m.
14. A method of determining whether an individual has reduced ability to form platelet thrombi due to GPIIb/IIIa blockade, comprising the steps of:
a) obtaining a blood sample from the individual being assessed;
b) mixing the blood sample with 1) an anticoagulant; 2) sufficient buffer to maintain the pH and salt concentration of the anticoagulated blood within a range suitable for platelet aggregation; 3) a peptide immobilized on a polymeric bead, said peptide comprising a platelet GPIIb/IIIa receptor ligand with an RGD recognition sequence; and 4) a thrombin receptor activating peptide resistant to aminopeptidase M inactivation;
c) agitating the mixture formed in b) for a period of time sufficient for unblocked platelet GPIIb/IIIa receptors to bind with the platelet GPIIb/IIIa receptor ligands on the beads; and
d) assessing platelet-mediated agglutination in the agitated mixture, wherein the absence of agglutination indicates that the individual has reduced ability to form platelet thrombi.
15. A method of claim 14 wherein the proportions of blood, anticoagulant, buffer, ligand coated polymeric beads, and thrombin receptor activating peptide are adjusted so that the absence of agglutination within about two minutes after agitating the mixture indicates that the individual has reduced ability to form platelet thrombi due to GPIIb/IIIa blockade.
16. A method of determining the degree of GPIIb/IIIa receptor blockade in a blood sample, comprising the steps of:
a) obtaining a blood sample from an individual being assessed;
b) mixing the blood sample with 1) an anticoagulant; 2) sufficient buffer to maintain the pH and salt concentration of the anticoagulated blood within a range suitable for platelet aggregation; and 3) a platelet GPIIb/IIIa receptor ligand immobilized on a solid surface;
c) agitating the mixture formed in b) for a period of time sufficient for unblocked platelet GPIIb/IIIa receptors to bind with the platelet GPIIb/IIIa receptor ligands on said solid surface; and
d) assessing platelet-mediated agglutination in the agitated mixture, wherein the absence of agglutination indicates that about 80% or more of the GPII;b/IIIa receptors are blocked, and the presence of normal agglutination indicates that less than about 50% of the GPIIb/IIIa receptors are blocked.
17. The method of claim 16 wherein the GPIIb/IIIa receptor ligand is selected from the group consisting of fibrinogen, monoclonal antibody 10E5, monoclonal antibody c7E3, von Willebrand factor, fibronectin, vitronectin, and synthetic ligands having an arginine-glycine-aspartic acid (RGD) GPIIb/IIIa binding sequence.
18. The method of claim 16 further comprising the addition of a thrombin receptor activator in step b).
19. The method of claim 18 wherein the thrombin receptor activator is a thrombin receptor activating peptide.
20. The method of claim 19 further comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
21. The method of claim 19 wherein the thrombin receptor activating peptide is selected from the group consisting of (SEQ ID NOS: 1, 2, 4, and 7).
22. The method of claim 21 further Comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
23. The method of claim 19 wherein the thrombin receptor activating peptide comprises a peptide resistant to inactivation by plasma aminopeptidase M.
24. The method of claim 23 wherein the thrombin receptor activating peptide comprises an N-terminal isoSer peptide.
25. The method of claim 24 wherein the N-terminal isoSer peptide is selected from the group consisting of (SEQ ID NOS: 3, 5, 6, and 8).
26. The method of claim 25 wherein the N-terminal isoSer peptide comprises isoSer-Phe-Leu-Leu-Arg-Asn (SEQ ID NO:3).
27. The method of claim 16 wherein the solid surface comprises glass microparticles or small polymeric beads, the surface of said microparticles or beads modified with a GPIIb/IIIa receptor ligand.
28. The method of claim 27 wherein the small polymeric beads have diameters from about 1 to about 6 .mu.m.
29. A method of determining the degree of GPIIb/IIIa receptor blockade in the blood of an individual, comprising the steps of:
a) obtaining a blood sample from the individual being assessed;
b) mixing the blood sample with 1) an anticoagulant; 2) sufficient buffer to

maintain the pH and salt concentration of the anticoagulated blood within a range suitable for platelet aggregation; 3) a peptide immobilized on a polymeric bead, said peptide comprising a platelet GPIIb/IIIa receptor ligand with an RGD recognition sequence; and 4) a thrombin receptor activating peptide resistant to aminopeptidase M inactivation;
c) agitating the mixture formed in b) for a period of time sufficient for unblocked platelet GPIIb/IIIa receptors to bind with the platelet GPIIb/IIIa receptor ligands on the beads; and
d) assessing platelet-mediated agglutination in the agitated mixture, wherein the absence of agglutination indicates that greater than about 80% of GPIIb/IIIa receptors are blocked and normal agglutination indicates that less than about 50% of the GPIIb/IIIa receptors are blocked.
30. A method of claim 29 wherein the proportions of blood, anticoagulant, buffer, ligand coated polymeric beads, and thrombin receptor activating peptide are adjusted so that the absence of agglutination within about two minutes after agitating the mixture indicates that greater than about 80% of the GPIIb/IIIa receptors are blocked.
31. A method of diagnosing Glanzmann thrombasthenia or thrombocytopenia in an individual, comprising the steps of:
a) obtaining a blood sample from an Individual being assessed for Glanzmann thrombasthenia or thrombocytopenia at a time when the individual has not been administered an agent that blocks platelet GPIIb/IIIa receptors;
b) mixing the blood sample with 1) an anticoagulant; 2) sufficient buffer to maintain the pH and salt concentration of the anticoagulated blood within a range suitable for platelet aggregation; and 3) a platelet GPIIb/IIIa receptor ligand immobilized on a solid surface;
c) agitating the mixture formed in b) for a period of time sufficient for unblocked platelet GPIIb/IIIa receptors to bind with the platelet GPIIb/IIIa receptor ligands on said solid surface; and
d) assessing platelet-mediated agglutination in the agitated mixture, wherein the absence of agglutination is indicative of Glanzmann thrombasthenia or thrombocytopenia.
32. The method of claim 31 wherein the GPIIb/IIIa receptor ligand is selected from the group consisting of fibrinogen, monoclonal antibody 10E5, monoclonal antibody c7E3, von Willebrand factor, fibronectin, vitronectin, and synthetic ligands having an arginine-glycine-aspartic acid (RGD) GPIIb/IIIa binding sequence.
33. The method of claim 31 further comprising the addition of a thrombin receptor activator in step b).
34. The method of claim 33 wherein the thrombin receptor activator is a thrombin receptor activating peptide.
35. The method of claim 34 further comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
36. The method of claim 34 wherein the thrombin receptor activating peptide is selected from the group consisting of (SEQ ID NOS: 1, 2, 4, and 7).
37. The method of claim 36 further comprising adding a plasma aminopeptidase M inhibitor to the mixture of blood, anticoagulant, buffer, GPIIb/IIIa receptor ligand, and thrombin receptor activating peptide.
38. The method of claim 34 wherein the thrombin receptor activating peptide comprises a peptide resistant to inactivation by plasma aminopeptidase M.
39. The method of claim 38 wherein the thrombin receptor activating peptide comprises an N-terminal isoSer peptide.
40. The method of claim 35 wherein the N-terminal isoSer peptide is selected from the group consisting of (SEQ ID NOS: 3, 5, 6, and 8).
41. The method of claim 40 wherein the N-terminal isoSer peptide comprises isoSer-Phe-Leu-Leu-Arg-Asn (SEQ ID NO:3).
42. The method of claim 31 wherein the solid surface comprises glass microparticles or small polymeric beads, the surface of said microparticles or beads modified with a GPIIb/IIIa receptor ligand.
43. The method of claim 42 wherein the small polymeric beads have diameters from about 1 to about 6 .mu.m.

SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1966-2001/Jun W4
(c) format only 2001 Dialog Corporation
*File 155: This file has been reloaded. Accession numbers have changed.
Please see Help News155 for further details.
File 162:CAB HEALTH 1983-2001/May
(c) 2001 CAB INTERNATIONAL
*File 162: Truncating CC codes is recommended for full retrieval.
See Help News162 for details.
File 349:PCT Fulltext 1983-2001/UB=20010614, UT=20010531
(c) 2001 WIPO/MicroPat
File 342:Derwent Patents Citation Indx 1978-01/200129
(c) 2001 Derwent Info Ltd
*File 342: Price changes as of 1/1/01. Please see HELP RATES 342.
File 347:JAPIO OCT 1976-2001/Feb(UPDATED 010604)
(c) 2001 JPO & JAPIO
*File 347: JAPIO data problems with year 2000 records are now fixed.
Alerts have been run. See HELP NEWS 347 for details.
File 348:EUROPEAN PATENTS 1978-2001/Jun W03
(c) 2001 European Patent Office
File 148:Gale Group Trade & Industry DB 1976-2001/Jun 22
(c)2001 The Gale Group
File 322:Polymer Online
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File 144:Pascal 1973-2001/Jun W4
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*File 156: This file is closed (no updates). For toxicology search
strategy and changes to the file please see Help News156.

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S1 217 PLATELET? (100N) THERMOPLASTIC?
S2 212 RD (unique items)
S3 0 S S2/1998:2001
S4 212 S2 NOT S3
S5 50 TARGET - S4
S6 162 S4 NOT S5
S7 50 TARGET - S6
S8 112 S6 NOT S7
S9 50 TARGET - S8
S10 62 S8 NOT S9
S11 50 TARGET - S10
?t s7/3,kwic/17 18 24 32 33

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Search Results -

Terms	Documents
l26 and (l8 or l9)	17

Database:
- US Patents Full-Text Database
- US Pre-Grant Publication Full-Text Database
- JPO Abstracts Database
- EPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Refine Search: `126 and (18 or 19)` Clear

Search History

Today's Date: 6/25/2001

DB Name	Query	Hit Count	Set Name
USPT	l26 and (l8 or l9)	17	L27
USPT	l18 same (monolithic or mono-lithic or dispers$)	3510	L26
USPT	l11 and l18.clm.	13	L25
USPT	l23 and l18.clm.	3	L24
USPT	l11 and l13.clm.	2061	L23
USPT	l20 not I	2	L22
USPT	l19 and l13 not polymer	141	L21
USPT	l19 and l13	293	L20
USPT	l18 and (l1 or l8 or l9)	294	L19
USPT	binding near5 agent	28816	L18
USPT	(l9 or l8 or platelet) near25 l15	710	L17
USPT	(l9 or l8 or platelet) same l15	1539	L16
USPT	(capsul$ or encapsul$ or dispers$ or monolith$ or mono-lith$)	467026	L15
USPT	l13 same (l9 or l8 or platlet)	237	L14
USPT	(l3 or l4 or thermoplastic or thermoplastic)	1480783	L13
USPT	l11 and l10	2	L12
USPT	monolithic.clm. or mono-lithic.clm.	6940	L11
USPT	(l8 or l9 or l1) and (l3 or l4 or thermoplastic or thermo-plastic)	1731	L10
USPT	gmp-140 or gmp140 or gplb or gp-ib or gp1b or gp-lb or gpiv or gp-iv or gplv or gplv or gp1v or gp-1v or gpib/ix or gp1b/1x or gpIIa/IIa	1329	L9
USPT	platelet near3 (glycoprotein or glyco-protein)	731	L8
USPT	platlet near3 (glycoprotein or glyco-protein)	0	L7
USPT	(l3 or l4).ti,clm. and l1.ti,clm.	14	L6
USPT	(l3 or l4) and l1	389	L5
USPT	polyvinylidene or polyacrylonitrile or polyvinylidene or polyacrylonitrile or polymethyl-methacrylate or polystyrene-polyacrylonitrile or polyvinylidene-polyacrylonitrile	33318	L4
USPT	polyvinylidene or polyacrylonitrile or olyvinylidene or polyacrylonitrile or polymethyl-methacrylate or polystyrene-polyacrylonitrile or polymer is polyvinylidene-polyacrylonitrile.	1449872	L3
USPT	l1 and thermoplast$	3	L2
USPT	gp11b/111a or gpllb/llla or gp2b/3a or gpiib/iiia	397	L1

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Search Results -

Terms	Documents
l1 and (integrin or platelet or gpll$ or glycoprotein or receptor)	35

Database: US Patents Full-Text Database
US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Refine Search: `l1 and (integrin or platelet or gpll$ or glycoprotein or receptor)` Clear

Search History

Today's Date: 6/25/2001

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USPT	molecular near2 imprint$	68	L1

updated search

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N3           362   399: CA SEARCH(R)_1967-2001/UD=13426
N4           270   144: Pascal_1973-2001/Jun W4
N5           216   305: Analytical Abstracts_1980-2001/Jun W1
N6           170    73: EMBASE_1974-2001/Jun W3
N7           150     5: Biosis Previews(R)_1969-2001/Jun W3
N8           144    94: JICST-EPlus_1985-2001/May W4
N9           137*  348: EUROPEAN PATENTS_1978-2001/Jun W03
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N12           99    71: ELSEVIER BIOBASE_1994-2001/Jun W1
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N14           86    65: Inside Conferences_1993-2001/Jun W2
N15           69    98: General Sci Abs/Full-Text_1984-2001/May
N16           66   654: US PAT.FULL._1990-2001/Jun 19
N17           50    99: Wilson Appl. Sci & Tech Abs_1983-2001/May
N18           41   151: HealthSTAR_1975-2000/Dec
N19           39*  349: PCT Fulltext_1983-2001/UB=20010614, UT=20010531
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N24           17     2: INSPEC_1969-2001/Jun W4
N25           15   340: CLAIMS(R)/US PATENT_1950-01/Jun 19
N26           15*  345: Inpadoc/Fam.& Legal Stat_1968-2001/UD=200124
N27           14    35: Dissertation Abs Online_1861-2001/Jul
N28           14   315: ChemEng & Biotec Abs_1970-2001/May
N29           13   148: Gale Group Trade & Industry DB_1976-2001/Jun 22
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N34            10    53: FOODLINE(R) Food Science & Technology_1972-2001/J
N35            10   636: Gale Group Newsletter DB(TM)_1987-2001/Jun 22
N36             9   357: Derwent Biotechnology Abs_1982-2001/Jul B1
N37             8   103: Energy SciTec_1974-2001/Jun B1
N38             8   172: EMBASE Alert_2001/Jun W3
N39             8   342: Derwent Patents Citation Indx_1978-01/200129
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N44            7   266: FEDRIP_2001/Jun
N45            6   285: BioBusiness(R)_1985-1998/Aug W1
N46            5    20: World Reporter_1997-2001/Jun 25
N47            5    51: Food Sci.&Tech.Abs_1969-2001/Aug W3
N48            5    96: FLUIDEX_1972-2001/Jun
N49            5   149: TGG Health&Wellness DB(SM)_1976-2001/Jun W3
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N54            4   286: Biocommerce Abs.& Dir._1981-2001/Jun B1
N55            4   764: BCC Market Research_1989-2001/May
N56            3   108: AEROSPACE DATABASE_1962-2001/JUN
N57            3   319: Chem Bus NewsBase_1984-2001/Jun 25
N58            3   322: Polymer Online_
N59            2   119: Textile Technol.Dig._1978-2001/Jun
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N64            2   369: New Scientist_1994-2001/Jun W1
N65            2   649: Gale Group Newswire ASAP(TM)_2001/Jun 20
N66            2   653: US Patents Fulltext_1980-1989
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N73            1    41: Pollution Abs_1970-2001/Jul
N74            1    42: Pharmaceuticl News Idx_1974-2001/Jun W3
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N76            1    89: GeoRef_1785-2001/Jun B2
N77            1   117: Water Resour.Abs._1967-2001/May
N78            1   129: PHIND(Archival)_1980-2001/Jun W3
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N82            1   292: GEOBASE(TM)_1980-2001/Jun
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N84            1   441: ESPICOM Pharm&Med DEVICE NEWS_2001/May W1
N85            1   455: Drug News & Perspectives_1992-2001/May
N86            1   457: The Lancet_1986-2000/Oct W1
N87            1   553: Wilson Bus. Abs. FullText_1982-2001/May
N88            1   613: PR Newswire_1999-2001/Jun 25
N89            1   621: Gale Group New Prod.Annou.(R)_1985-2001/Jun 22
N90            1   652: US Patents Fulltext_1971-1979
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N93            0    28: Oceanic Abst._1964-2001/Jul
N94            0    29: Meteor.& Geoastro.Abs._1970-2001/Jun
N95            0    33: Aluminium Ind Abs_1968-2001/Jul
N96            0    40: Enviroline(R)_1975-2001/May
N97            0    43: Health News Daily_1990-2001/Jun 12
N98            0    48: SPORTDiscus_1962-2001/Jun
N99            0    49: PAIS Int._1976-2001/May
N100           0    52: TSCA Chemical Substances Inventory_2001/Feb,
   91 files have one or more items; file list includes 287 files.
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L25 ANSWER 18 OF 18 WPIDS COPYRIGHT 1998 DERWENT INFORMATION LTD
AN 73-36473U [26] WPIDS
TI Hot pressing **thermoplastics** sheet - onto other material using heat activated adhesive.
DC A35 P73
PA (ING-N) INGHAM AND CO LTD RE
CYC 5
PI DE 2259800 A (7326)*
NL 7216441 A (7326)
JP 48066170 A (7347)
GB 1384712 A 750219 (7508)
US 3879251 A 750422 (7518)
PRAI GB 71-56658 711207
AB DE 2259800 A UPAB: 930831
A method of laminating a **thermoplastics** sheet onto a sheet of another material (opt. contg. some **thermoplastics**) utilises **thermoplastics** adhesive or **thermoplastics** -like adhesive, i.e. adhesive which is activated at 120 degrees - 180 degrees C. The two sheets and the adhesive are pressed between the plates of a press, utilising a flat, sheet-like electrical heating element inserted between one of the sheets and the adjacent plate of the press. The pref. rating for the electrical heating sheet is 45 - 125 kw/m2, applied for 4 - 18 secs. The prefd. appts. comprises a press in which the heating element is an electrical resistance net, **embedded** in a **binding agent** of ceramic adhesive, silicone resin or phenolic resin, to a total thickness of 0.76 - 1.5 cm. An insulating layer, of asbestos or glass-fibre-reinforced material, may be incorporated between the heating element and the adjacent plate of the press.